

Copper-catalyzed direct borylation of alkyl, alkenyl and aryl halides with B(dan)

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Hiroto Yoshida,* Yuki Takemoto, Shintaro Kamio, Itaru Osaka and Ken Takaki

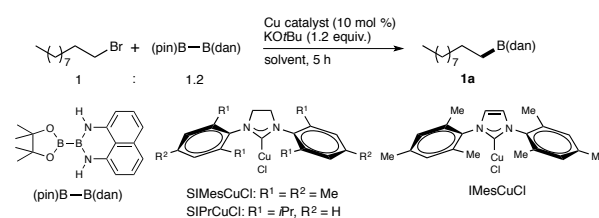
Substitutional borylation of C(sp³ or sp²)-halogen bonds with an unsymmetrical diboron [(pin)B-B(dan)] was found to proceed smoothly under copper catalysis. A variety of masked alkyl-, alkenyl- and arylboron compounds [R-B(dan)] were straightforwardly accessible with high functional group compatibility in high yield.

Introduction

Boron-masking-unmasking strategy has assuredly opened up a new vista of modern organoboron chemistry,^{1,2} especially in accessing such invaluable molecules as oligoarenes^{1a-d,f} and natural products^{2a-c,h,k,n} via iterative cross-coupling processes. The representative masked organoboron compounds used for this purpose are R-B(dan) (dan: 1,8-diaminonaphthalene) and R-B(mida) (mida: *N*-methyliminodiacetic acid), being generally prepared by replacement of substituents on preformed organoboronic acids or esters by dan^{1a,b,3} or mida,² and thus the structural diversity of the available masked organoboron compounds are mainly dependent on those of organoboronic acids and esters that can be synthesized by the existing methods. Because some organoboronic acids/esters are intractable and unstable, development of direct way of installing the masked boryl moieties into organic frameworks^{1c-f,4} is of urgent importance in synthetic organic chemistry.

We have recently devoted our attention to developing potential catalysis of a masked borylcopper species [Cu-B(dan)] arising from selective σ -bond metathesis between an unsymmetrical diboron [(pin)B-B(dan)]^{1e,5} and Cu-OR, and have demonstrated that this borylcopper species has an apparent affinity for unsaturated carbon-carbon bonds, leading to three-component hydroboration⁶ and borylstannylation⁷ of alkynes and alkenes using an alcohol or a tin alkoxide⁸ as an electrophile.^{9,10} In view of latent nucleophilicity of the borylcopper species derived from Cu^{δ+}-B(dan)^{δ-} polarization,¹¹ we envisaged that electrophilic carbon center of organic halides should exhibit high reactivity toward the masked borylcopper species. We report herein on the copper-catalyzed formal nucleophilic substitution of organic halides with a B(dan) moiety, which provides direct access to

Table 1 Optimization of the reaction conditions^a



Entry	Cu cat.	Solvent	Temp. (°C)	Yield (%) ^b
1	(PPh ₃) ₃ CuCl	THF	50	71
2 ^c	CuCl, xantphos	THF	50	57
3	SIPrCuCl	THF	50	69
4	IMesCuCl	THF	50	75
5	SIMesCuCl	THF	50	80
6	SIMesCuCl	Toluene	50	58
7	SIMesCuCl	DMF	50	77
8	none	THF	50	0
9 ^d	SIMesCuCl	THF	50	0
10 ^e	SIMesCuCl	THF	10	87
11 ^f	SIMesCuCl	THF	50	41
12 ^g	SIMesCuCl	THF	10	91

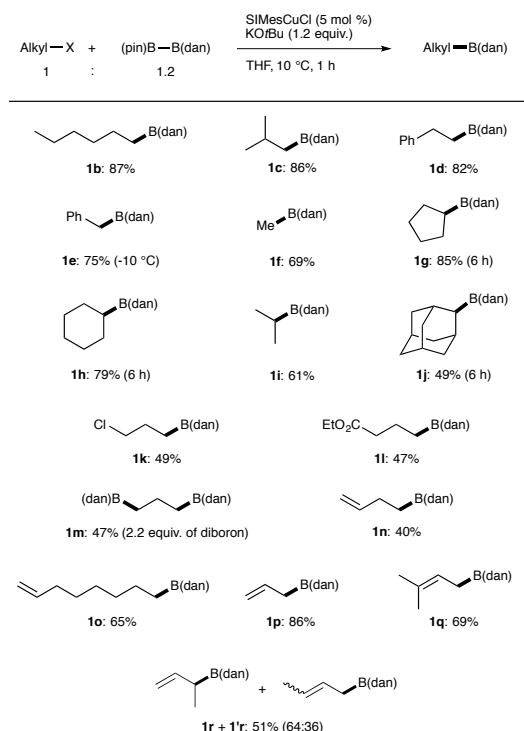
^a Conditions: 1-bromodecane (0.30 mmol), diboron (0.36 mmol), KOtBu (0.36 mmol), Cu catalyst (0.030 mmol), solvent (1 mL), 5 h. ^b Isolated yield. ^c CuCl/xantphos = 1. ^d K₃PO₄ (0.30 mmol) was used instead of KOtBu. ^e SIMesCuCl: 5 mol %, time: 1 h. ^f SIMesCuCl: 1 mol %. ^g SIMesCuCl: 1 mol %, time: 14 h.

diverse masked alkyl, alkenyl and arylboron compounds.¹²

Results and discussion

Our effort was initially focused upon the reaction of 1-bromodecane with (pin)B-B(dan) to observe that the C-Br bond was substituted by B(dan) in the presence of KOtBu and (PPh₃)₃CuCl catalyst, giving a 71% yield of **1a** without any formation of the respective pinacol boronate (entry 1, Table 1).^{12b-e} Other ligands (xantphos and NHC) and solvents could also be used for this transformation, and a combination of SIMes and THF turned out to be optimum (entries 2–7). No substitution occurred in the absence of the copper catalyst

Department of Applied Chemistry, Graduate School of Engineering, Hiroshima University, Higashi-Hiroshima 739-8527, Japan. E-mail: yhiroto@hiroshima-u.ac.jp
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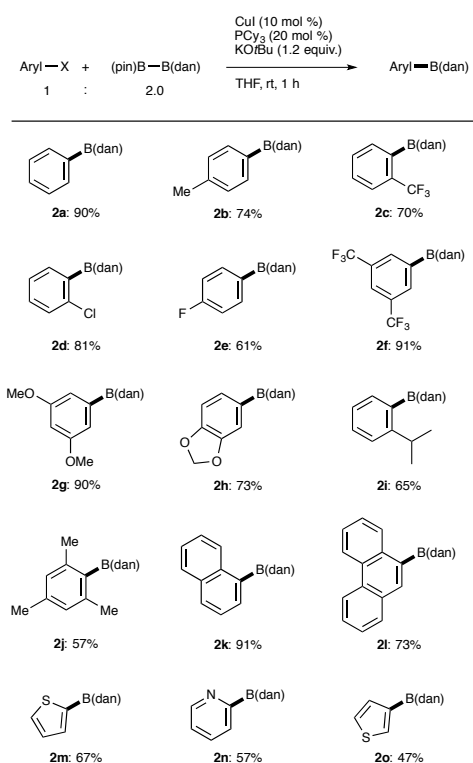
Table 2 Scope of alkyl halides^a

^a Isolated yield. Conditions: alkyl halide (0.30 mmol), diboron (0.36 mmol), KOtBu (0.36 mmol), SiMesCuCl (0.015 mmol), THF (1 mL), 10 °C, 1 h.

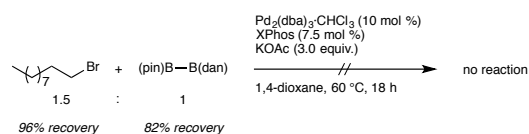
(entry 8), and the use of a weak base (K_3PO_4) also inhibited the reaction (entry 9). By conducting the reaction at 10 °C, the amount of the catalyst was found to be reduced to 5 mol % and 1 mol % without loss of the product yield, although prolonged reaction time was necessary for completion in the latter case (entries 10–12).

A variety of primary alkyl halides bearing a C–Br or a C–I bond (I for **1b** and **1f**, Br for the others) were readily convertible into the corresponding masked alkylboron compounds (**1b–1f**) under the optimized conditions (Table 2), and the reaction of secondary alkyl bromides (**1g–1j**) smoothly proceeded regardless of the steric hindrance, whereas a desired product was not formed at all with *tert*-butyl bromide. A C–Cl bond (**1k**) and an ester moiety (**1l**) were tolerable throughout the reaction, demonstrating the high functional group compatibility; on the other hand, 1,3-dibromopropane (**1m**) underwent dual borylation. A masked borylcopper species [Cu–B(dan)] showed higher affinity toward a C–Br bond of 4-bromo-1-butene (**1n**) and 8-bromo-1-octene (**1o**), where cyclized products arising from intramolecular carboboration of a C–C double bond were not generated.^{12g,13} Furthermore, simple allyl bromide (**1p**) could also participate in the reaction, and exclusive α -substitution took place with prenyl bromide (**1q**), while the reaction of crotyl bromide (*E*:*Z* = 84:16) afforded a mixture of α - (**1'r**) and γ -products (**1r**).

The versatility of the substitution reaction with the B(dan) moiety was further expanded by application to C(sp²)–X bonds (Table 3). Thus, treatment of bromobenzene, (pin)B–B(dan) and KOtBu with CuI–PCy₃ as an optimum catalyst¹⁴ furnished

Table 3 Scope of aryl halides^a

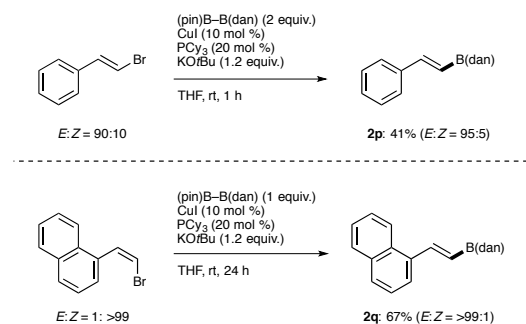
^a Isolated yield. Conditions: aryl halide (0.30 mmol), diboron (0.60 mmol), KOtBu (0.36 mmol), CuI (0.030 mmol), PCy₃ (0.060 mmol), THF (1 mL), rt, 1 h.



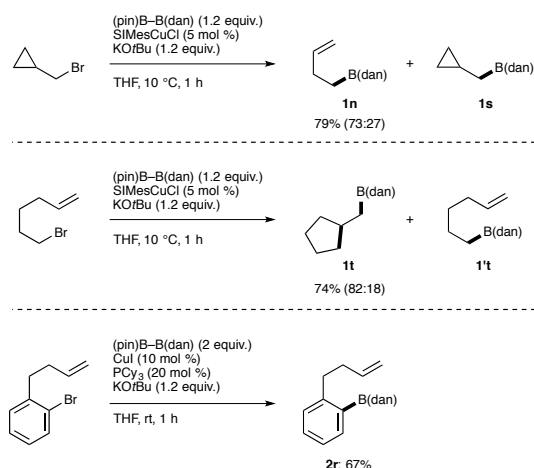
Scheme 1 Pd-catalyzed reaction of 1-bromodecane with (pin)B–B(dan)

Ph–B(dan) (**2a**) in 90% yield. Monosubstituted aryl bromides (or iodide for **2b**) having a methyl, trifluoromethyl (**2c**), chloro (**2d**) or fluoro (**2e**) moiety could efficiently be transformed into masked aryl boron compounds, in which the Ar–Cl (or F) bond remained intact. In addition to disubstituted aryl bromides which also provided good yields of the products (**2f–2h**), sterically bulky (**2i** and **2j**), polycyclic (**2k** and **2l**) and heterocyclic (**2m–2o**) aryl bromides readily underwent the substitution. A palladium-catalyzed coupling reaction of aryl halides with (pin)B–B(dan) was reported previously,^{4e} however this system has turned out to be inefficient for an alkyl halide (Scheme 1), demonstrating the wide applicability of the present reaction.

The reaction was also found to be applicable to alkenyl bromides (Scheme 2), which would give some insights into the reaction pathway: both (*E*)- and (*Z*)-alkenyl bromides preferentially provided (*E*)-alkenyl boron compounds (**2p** and **2q**), implying the intermediacy of an alkenyl radical in the present substitution, because a parent vinyl radical has been reported to be rapidly interconverting ($k = 4.0 \times 10^{10} \text{ s}^{-1}$ at 300 K) due to an inversion barrier as low as 3 kcal/mol.¹⁵ The



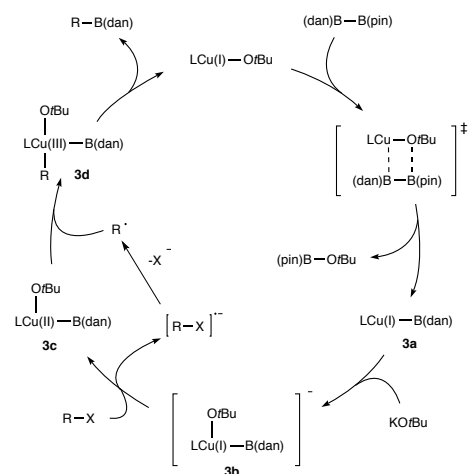
Scheme 2 Stereochemistry with alkenyl bromides



Scheme 3 Radical clock reactions

involvement of a radical intermediate in the $C(sp^3)-Br$ substitution was also strongly supported by the reaction of cyclopropylmethyl bromide¹⁶ or 6-bromo-1-hexene (Scheme 3), leading to the predominant formation of a ring-opened product (**1n**, rate constant for ring opening: $k = 8.6 \times 10^7 \text{ s}^{-1}$ at 298 K)¹⁷ or a cyclized product (**1t**, rate constant for ring closure: $k = 2.3 \times 10^5 \text{ s}^{-1}$ at 298 K).^{18,19} In contrast, 2-(3-butenyl)phenyl bromide afforded the simple substitution product (**2r**) in 67% yield, although the respective aryl radical is apt to undergo cyclization (rate constant for ring closure: $k = 5.0 \times 10^8 \text{ s}^{-1}$ at 323 K).²⁰

The above results indicate that the present reaction includes one-electron reduction of organic halides as a key step, and thus we propose a catalytic cycle, which commences with the formation of a masked borylcopper species $[Cu-B(dan)]$ (**3a**) via selective interaction between Lewis acidic B(pin) and Lewis basic OtBu in σ -bond metathesis step (Scheme 4).^{6,7,9} Then KOtBu coordinates to **3a** to generate an electron-rich borylcuprate species (**3b**), which may serve as a one-electron reductant for an organic halide.^{12g,21} Subsequent elimination of X^- from the resulting radical anion which generates an isomerizable free radical (*cf.* Schemes 2 and 3), followed by combination of the radical with $[tBuO-Cu(II)-B(dan)]$ (**3c**) gives a Cu(III) complex (**3d**).²² Finally, **3d** undergoes reductive elimination to afford a masked organoboron compounds with regeneration of $Cu-OtBu$.^{23,24} The exceptional result with 2-(3-butenyl)phenyl bromide may



Scheme 4 Proposed catalytic cycle

be construed that an aryl radical was instantaneously captured by **3c** before ring closure or that a isomerization-resistant radical anion²⁵ directly reacted with **3c**.

Conclusions

In conclusion, we have developed the direct and potent method for installing a B(dan) moiety into organic frameworks through the copper-catalyzed substitution of $C(sp^3 \text{ or } sp^2)-X$ bonds which gives diverse masked alkyl-, alkenyl- and arylboron compounds of high synthetic utility, and have demonstrated that the reaction includes one-electron transfer process, being in marked contrast to the cases of the previous copper-catalyzed B(dan)-installing reactions into unsaturated C–C bonds.^{6,7} Further studies on the catalytic utilization of the $Cu-B(dan)$ species for the direct synthesis of masked organoboron compounds as well as on the details of the mechanism are in progress.

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